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0314131.4

1. Your reference 101075-1 GB

18 JUN 2003

2. Patent application number  
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18JUN03 E815966-3 D02934  
P01/7700 0.00-0314131.4

3. Full name, address and postcode of the or of each applicant (underline all surnames)

AstraZeneca AB  
SE-151 85 Sodertalje  
Sweden

Patents ADP number (if you know it)

782244800

If the applicant is a corporate body, give the country/state of its incorporation

Sweden

4. Title of the invention

THERAPEUTIC AGENTS

5. Name of your agent (if you have one)

Thomas Kerr MILLER

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

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Cheshire SK10 4TG

7822471002

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Number of earlier application

Date of filing  
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Description 33

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**Therapeutic Agents****Field of the invention**

5 The present invention relates to certain novel salts of 3-phenyl-2-arylalkylthiopropionic acid derivatives, to processes for preparing such compounds, to their utility in treating clinical conditions including lipid disorders (dyslipidemias) whether or not associated with insulin resistance and other manifestations of the metabolic syndrome, to methods for their therapeutic use and to pharmaceutical compositions containing them.

10

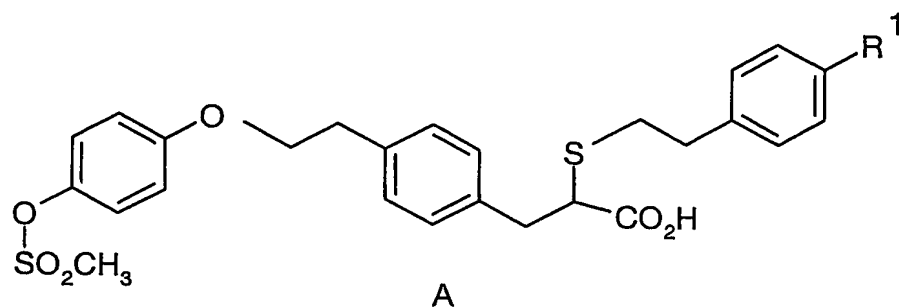
**Background of the invention**

The metabolic syndrome including type 2 diabetes mellitus, refers to a cluster of manifestations including insulin resistance with accompanying hyperinsulinaemia, possibly  
15 type 2 diabetes mellitus, arterial hypertension, central (visceral) obesity, dyslipidaemia observed as deranged lipoprotein levels typically characterised by elevated VLDL (very low density lipoproteins), small dense LDL particles and reduced HDL (high density lipoprotein) concentrations and reduced fibrinolysis.

20 Recent epidemiological research has documented that individuals with insulin resistance run a greatly increased risk of cardiovascular morbidity and mortality, notably suffering from myocardial infarction and stroke. In type 2 diabetes mellitus atherosclerosis related conditions cause up to 80% of all deaths.

25 In clinical medicine there is awareness of the need to increase the insulin sensitivity in patients with the metabolic syndrome and thus to correct the dyslipidaemia which is considered to cause the accelerated progress of atherosclerosis. However, currently this is not a universally accepted diagnosis with well-defined pharmacotherapeutic indications.

30 Co-pending PCT application No. PCT/GB02/05743 discloses compounds of formula A



wherein  $R^1$  represents chloro, fluoro or hydroxy as well as optical isomers and racemates thereof as well as pharmaceutically acceptable salts, prodrugs, solvates and crystalline forms thereof which are selective PPAR $\alpha$  modulators (for a review of the PPARs (peroxisome proliferator-activated receptors) see T. M. Willson et al, J Med Chem 2000, Vol 43, 527). These compounds are effective in treating conditions associated with insulin resistance. Specific pharmaceutically-acceptable salts of compounds of the formula A are not disclosed in PCT/GB02/05743. Further, no information is provided in relation to how crystalline forms of compounds of the formula A, and particularly salts thereof, may be prepared. The (-) enantiomer of the compound in which  $R^1$  represents hydroxy is prepared as the free acid in this application. However, this compound is a thick oil with a syrup-like consistency and is thus not suitable for use in pharmaceutical formulations since it is not mobile. Therefore there exists a need for a solid derivative of this compound which has physical and chemical properties suitable for use in pharmaceutical formulations. Many salts were tried but most of these either could not be formed in the solid state or were amorphous with a low glass transition temperature. Salts with suitable properties for pharmaceutical formulation have now been found.

In the formulation of drug compositions, it is important for the drug substance to be in a form in which it can be conveniently handled and processed. This is of importance, not only from the point of view of obtaining a commercially-viable manufacturing process, but also from the point of view of subsequent manufacture of pharmaceutical formulations comprising the active compound.

Further, in the manufacture of drug compositions, it is important that a reliable, reproducible and constant plasma concentration profile of drug is provided following administration to a patient.

Chemical stability, solid state stability, and "shelf life" of the active ingredients are also very important factors. The drug substance, and compositions containing it, should preferably be capable of being effectively stored over appreciable periods of time, without exhibiting a significant change in the active component's physico-chemical characteristics (e.g. its chemical composition, density, hygroscopicity and solubility).

Moreover, it is also important to be able to provide drug in a form which is as chemically pure as possible.

The skilled person will appreciate that, typically, if a drug can be readily obtained in a stable form, such as a stable crystalline form, advantages may be provided, in terms of ease of handling, ease of preparation of suitable pharmaceutical formulations, and a more reliable solubility profile.

#### Description of the invention

The present invention provides a potassium salt or a sodium salt of (-)-2-([2-(4-hydroxyphenyl)ethyl]thio)-3-[4-(2-[4-[(methylsulfonyl)oxy]phenoxy)ethyl]phenyl]propanoic acid.

According to a further aspect of the invention there is provided a compound of the invention in substantially crystalline form.

It is possible to produce compounds of the invention in forms which are greater than 80% crystalline, by "substantially crystalline" but also included are forms greater than 20%, preferably greater than 30%, and more preferably greater than 40% (e.g. greater than any of 50, 60, 70, 80 or 90%) crystalline.

According to a further aspect of the invention there is also provided a compound of the invention in partially crystalline form. By "partially crystalline" we include 5% or between 5% and 20% crystalline.

The degree (%) of crystallinity may be determined by the skilled person using X-ray powder diffraction (XRPD). Other techniques, such as solid state NMR, FT-IR, Raman spectroscopy, differential scanning calorimetry (DSC) and microcalorimetry, may also be used.

- 5 Compounds of the invention, and particularly crystalline compounds of the invention, may have improved stability when compared to compounds disclosed in PCT/GB02/05743.

The term “stability” as defined herein includes chemical stability and solid state stability.

- 10 By “chemical stability”, we include that it may be possible to store compounds of the invention in an isolated form, or in the form of a formulation in which it is provided in admixture with pharmaceutically acceptable carriers, diluents or adjuvants (e.g. in an oral dosage form, such as a tablet, capsule etc.), under normal storage conditions, with an insignificant degree of chemical degradation or decomposition.

15

- By “solid state stability”, we include that it may be possible to store compounds of the invention in an isolated solid form, or in the form of a solid formulation in which it is provided in admixture with pharmaceutically acceptable carriers, diluents or adjuvants (e.g. in an oral dosage form, such as a tablet, capsule etc.), under normal storage conditions, with an insignificant degree of solid state transformation (e.g. crystallisation, recrystallisation, solid state phase transition, hydration, dehydration, solvatisation or desolvatisation).
- 20

- Examples of “normal storage conditions” include temperatures of between minus 80 and plus 50°C (preferably between 0 and 40°C and more preferably room temperatures, such as 15 to 30°C), pressures of between 0.1 and 2 bars (preferably at atmospheric pressure), relative humidities of between 5 and 95% (preferably 10 to 60%), and/or exposure to 460 lux of UV/visible light, for prolonged periods (i.e. greater than or equal to six months). Under such conditions, compounds of the invention may be found to be less than 15%, more preferably less than 10%, and especially less than 5%, chemically degraded/decomposed, or solid state transformed, as appropriate. The skilled person will appreciate that the above-mentioned upper and lower limits for temperature, pressure and relative humidity represent extremes of normal storage conditions, and that certain combinations of these extremes will not be experienced during normal storage (e.g. a temperature of 50°C and a pressure of 0.1 bar).
- 25
- 30

It may be possible to crystallise salts of compounds of the present invention with or without the presence of a solvent system (e.g. crystallisation may be from a melt, under supercritical conditions, or achieved by sublimation). However, we prefer that crystallisation occurs from an appropriate solvent system.

5

According to a further aspect of the invention, there is provided a process for the preparation of a crystalline compound of the invention which comprises crystallising a compound of the invention from an appropriate solvent system. Suitable solvents include ethanol and toluene and mixtures thereof.

10

Crystallisation temperatures and crystallisation times depend upon the salt that is to be crystallised, the concentration of that salt in solution, and the solvent system which is used.

Crystallisation may also be initiated and/or effected by way of standard techniques, for example with or without seeding with crystals of the appropriate crystalline compound of the invention.

Different crystalline forms of the compounds of the invention may be readily characterised using X-ray powder diffraction (XRPD) methods, for example as described hereinafter.

20

In order to ensure that a particular crystalline form is prepared in the absence of other crystalline forms, crystallisations are preferably carried out by seeding with nuclei and/or seed crystals of the desired crystalline form in substantially complete absence of nuclei and/or seed crystals of other crystalline forms. Seed crystals of appropriate compound may be prepared, for example, by way of slow evaporation of solvent from a portion of solution of appropriate salt.

30

Compounds of the invention may be isolated using techniques which are well known to those skilled in the art, for example decanting, filtering or centrifuging.

Compounds may be dried using standard techniques.



Further purification of compounds of the invention may be effected using techniques, which are well known to those skilled in the art. For example impurities may be removed by way of recrystallisation from an appropriate solvent system. Suitable temperatures and times for the recrystallisation depend upon the concentration of the salt in solution, and upon the solvent  
5 system which is used.

When compounds of the invention are crystallised, or recrystallised, as described herein, the resultant salt may be in a form which has improved chemical and/or solid state stability, as mentioned hereinbefore.

10

Compounds of the invention have the advantage that they may be more efficacious, be less toxic, be longer acting, have a broader range of activity, be more potent, produce fewer side effects, be more easily absorbed, and/or have a better pharmacokinetic profile (e.g. higher oral bioavailability and/or lower clearance), than, and/or have other useful pharmacological,  
15 physical, or chemical, properties over, compounds known in the prior art. Compounds of the invention may have the further advantage that they may be administered less frequently than compounds known in the prior art.

Compounds of the invention may also have the advantage that they are in a form which  
20 provides for improved ease of handling. Further, compounds of the invention have the advantage that they may be produced in forms which may have improved chemical and/or solid state stability (including e.g. due to lower hygroscopicity). Thus, such compounds of the invention may be stable when stored over prolonged periods.

25 Compounds of the invention may also have the advantage that they may be crystallised in good yields, in a high purity, rapidly, conveniently, and at a low cost.

The compounds of the present invention have activity as medicaments, in particular the compounds are selective agonists of  $PPAR\alpha$ , that is, their  $EC_{50}$  for  $PPAR\alpha$  is at least ten  
30 times lower than their respective  $EC_{50}$  for  $PPAR\gamma$  wherein the  $EC_{50}$ s are measured and calculated as described in the assays later in this document. The compounds are potent and selective.

Specific compounds of the invention are:

- (-)-2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]propanoic acid potassium salt and
- 5 (-)-2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]propanoic acid sodium salt.

These salts have the advantage that they are crystalline and have good flow characteristics. These salts are suitable for pharmaceutical formulation.

10

It will be understood by those skilled in the art that where (-) occurs in this specification that the acid has a negative rotation when measured using the conditions and concentration described in the experimental section. It should be understood that the salts of the present invention may have (+) rotation provided that the absolute configuration of the salt is the

15 same as the configuration of the (-)-parent acid.

It will also be understood that the compounds of the present invention may exist in solvated, for example hydrated or solvated with ethanol, as well as unsolvated forms. It is to be understood that the present invention encompasses all such solvated and unsolvated forms.

20

In another aspect the invention provides the following embodiments.

A potassium salt of (-)-2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid characterised by an X-ray

25 powder diffraction pattern characterised by peaks with d-values at 9.3, 5.8, 4.65 and 4.53 Å.

A potassium salt of (-)-2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid having the XRPD pattern substantially as disclosed in figure A.

30

A sodium salt of (-)-2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid characterised by an X-ray powder diffraction pattern characterised by peaks with d-values at 12.8, 8.2, 4.16 and 4.08 Å.

A sodium salt of (-)-2-[[2-(4-hydroxyphenyl)ethyl]thio]-3-[4-(2-{4-  
[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid having the XRPD pattern  
substantially as disclosed in figure B.

5 Methods of preparation

The compounds of the invention may be prepared as outlined below. However, the invention  
is not limited to these methods.

Compounds of the invention may be prepared by reacting (-)-2-[[2-(4-hydroxyphenyl)-  
10 ethyl]thio]-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]-propanoic acid with  
either a potassium containing base, for example potassium hydroxide, or a sodium containing  
base, for example sodium hydroxide, in an inert solvent at a temperature in the range of 0-  
100°C and isolating the solid salt. The salt may be isolated by cooling the reaction solution  
and optionally seeding the solution with the desired product and/or concentrating the solution.  
15 Optionally the product may be isolated by adding an antisolvent to a solution of the product in  
an inert solvent. The solid may be collected by methods known to those skilled in the art for  
example filtration or centrifugation.

In another aspect the present invention provides the compound obtainable by reacting (-)-2-  
20 [[2-(4-hydroxyphenyl)ethyl]thio]-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}-  
ethyl)phenyl]propanoic acid and potassium hydroxide, in ethanol. Particularly an equivalent  
potassium hydroxide of is used.

In another aspect the present invention provides the compound obtainable by reacting (-)-2-  
25 [[2-(4-hydroxyphenyl)ethyl]thio]-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}-  
ethyl)phenyl]propanoic acid and sodium methoxide, in ethanol followed by addition of  
toluene. Particularly an equivalent of sodium methoxide is used.

The expression "inert solvent" refers to a solvent that does not react with the starting  
30 materials, reagents, intermediates or products in a manner which adversely affects the yield of  
the desired product.

### Pharmaceutical preparations

The compounds of the invention will normally be administered via the oral, parenteral, intravenous, intramuscular, subcutaneous or in other injectable ways, buccal, rectal, vaginal, transdermal and/or nasal route and/or via inhalation, in the form of pharmaceutical preparations in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

Suitable daily doses of the compound of the invention in therapeutical treatment of humans are about 0.0001-100 mg/kg body weight, preferably 0.001-10 mg/kg body weight.

Oral formulations are preferred particularly tablets or capsules which may be formulated by methods known to those skilled in the art to provide doses of the active compound in the range of 0.5mg to 500mg for example 1 mg, 3 mg, 5 mg, 10 mg, 25mg, 50mg, 100mg and 250mg.

According to a further aspect of the invention there is thus provided a pharmaceutical formulation including the compound of the invention in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

### Pharmacological properties

The compounds of the invention is useful for the prophylaxis and/or treatment of clinical conditions associated with inherent or induced reduced sensitivity to insulin (insulin resistance) and associated metabolic disorders (also known as metabolic syndrome). These clinical conditions will include, but will not be limited to, general obesity, abdominal obesity, arterial hypertension, hyperinsulinaemia, hyperglycaemia, type 2 diabetes and the dyslipidaemia characteristically appearing with insulin resistance. This dyslipidaemia, also known as the atherogenic lipoprotein profile, is characterised by moderately elevated non-esterified fatty acids, elevated very low density lipoprotein (VLDL) triglyceride rich particles, high Apo B levels, low high density lipoprotein (HDL) levels associated with low apoAI particle levels and high Apo B levels in the presence of small, dense, low density lipoproteins (LDL) particles, phenotype B.

The compounds of the present invention are expected to be useful in treating patients with combined or mixed hyperlipidemias or various degrees of hypertriglyceridemias and postprandial dyslipidemia with or without other manifestations of the metabolic syndrome.

5 Treatment with the present compoundss is expected to lower the cardiovascular morbidity and mortality associated with atherosclerosis due to their antidyslipidaemic as well as antiinflammatory properties. The cardiovascular disease conditions include macro-  
angiopathies of various internal organs causing myocardial infarction, congestive heart  
10 failure, cerebrovascular disease and peripheral arterial insufficiency of the lower extremities. Because of its insulin sensitizing effect the compound is also expected to prevent or delay the development of type 2 diabetes from the metabolic syndrome and diabetes of pregnancy. Therefore the development of long-term complications associated with chronic  
hyperglycaemia in diabetes mellitus such as the micro-angiopathies causing renal disease,  
15 retinal damage and peripheral vascular disease of the lower limbs are expected to be delayed. Furthermore the compound may be useful in treatment of various conditions outside the cardiovascular system whether or not associated with insulin resistance, like polycystic ovarian syndrome, obesity, cancer and states of inflammatory disease including  
neurodegenerative disorders such as mild cognitive impairment, Alzheimer's disease,  
20 Parkinson's disease and multiple sclerosis.

The compounds of the present invention are expected to be useful in controlling glucose levels in patients suffering from type 2 diabetes.

25 The present invention provides a method of treating or preventing dyslipidemias, the insulin resistance syndrome and/or metabolic disorders (as defined above) comprising the administration of a compound of the present invention to a mammal (particularly a human) in need thereof.

30 The present invention provides a method of treating or preventing type 2 diabetes comprising the administration of an effective amount of a compound of the present invention to a mammal (particularly a human) in need thereof.

In a further aspect the present invention provides the use of a compound of the present invention as a medicament.

In a further aspect the present invention provides the use of a compound of the present invention in the manufacture of a medicament for the treatment of insulin resistance and/or metabolic disorders.

### Combination Therapy

The compounds of the invention may be combined with another therapeutic agent that is useful in the treatment of disorders associated with the development and progress of atherosclerosis such as hypertension, hyperlipidaemias, dyslipidaemias, diabetes and obesity. The compound of the invention may be combined with another therapeutic agent that decreases the ratio of LDL:HDL or an agent that causes a decrease in circulating levels of LDL-cholesterol. In patients with diabetes mellitus the compound of the invention may also be combined with therapeutic agents used to treat complications related to micro-angiopathies.

A compound of the invention may be used alongside other therapies for the treatment of metabolic syndrome or type 2 diabetes and its associated complications, these include biguanide drugs, for example metformin, phenformin and buformin, insulin (synthetic insulin analogues, amylin) and oral antihyperglycemics (these are divided into prandial glucose regulators and alpha-glucosidase inhibitors). An example of an alpha-glucosidase inhibitor is acarbose or voglibose or miglitol. An example of a prandial glucose regulator is repaglinide or nateglinide.

In another aspect of the invention, a compound of the invention may be administered in association with another PPAR modulating agent. PPAR modulating agents include but are not limited to a PPAR alpha and/or gamma and /or delta agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable PPAR alpha and/or gamma agonists, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are well known in the art. These include the compounds described in WO 01/12187, WO 01/12612, WO 99/62870, WO 99/62872, WO 99/62871, WO 98/57941, WO

01/40170, J Med Chem, 1996, 39, 665, Expert Opinion on Therapeutic Patents, 10 (5), 623-634 (in particular the compounds described in the patent applications listed on page 634) and J Med Chem, 2000, 43, 527 which are all incorporated herein by reference. Particularly a PPAR alpha and/or gamma agonist refers to BMS 298585, clofibrate, fenofibrate, bezafibrate, 5 gemfibrozil and ciprofibrate; GW 9578, pioglitazone, rosiglitazone, rivoglitazone, balaglitazone, KRP-297, JTT-501, SB 213068, GW 1929, GW 7845, GW 0207, L-796449, L-165041 and GW 2433. Particularly a PPAR alpha and/or gamma agonist refers to (S)-2-ethoxy-3-[4-(2-{4-methanesulphonyloxy-phenyl}ethoxy)phenyl]propanoic acid and pharmaceutically acceptable salts thereof.

10

In addition a compound of the invention may be used in conjunction with a sulfonylurea for example: glimepiride, glibenclamide (glyburide), gliclazide, glipizide, gliquidone, chloropropamide, tolbutamide, acetohexamide, glycopyramide, carbutamide, glibonuride, glisoxepid, glybuthiazole, glibuzole, glyhexamide, glymidine, glypinamide, phenbutamide, 15 tolclamide and tolazamide. Preferably the sulfonylurea is glimepiride or glibenclamide (glyburide). More preferably the sulfonylurea is glimepiride. The present invention includes administration of a compound of the present invention in conjunction with one, two or more existing therapies described in this combination section. The doses of the other existing therapies for the treatment of type 2 diabetes and its associated complications will be those 20 known in the art and approved for use by regulatory bodies for example the FDA and may be found in the Orange Book published by the FDA. Alternatively smaller doses may be used as a result of the benefits derived from the combination. The present invention also includes a compound of the present invention in combination with a cholesterol-lowering agent. The cholesterol-lowering agents referred to in this application include but are not limited to 25 inhibitors of HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A reductase). Suitably the HMG-CoA reductase inhibitor is a statin selected from the group consisting of atorvastatin, bervastatin, cerivastatin, dalvastatin, fluvastatin, itavastatin, lovastatin, mevastatin, nicostatin, nivastatin, pravastatin and simvastatin, or a pharmaceutically acceptable salt, especially sodium or calcium, or a solvate thereof, or a solvate of such a salt. 30 A particular statin is atorvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. A more particular statin is atorvastatin calcium salt. A particularly preferred statin is, however, a compound with the chemical name (E)-7-[4-(4-

fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)-amino]-pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid, [also known as (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[N-methyl-N-(methylsulfonyl)-amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid ] or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt. The  
5 compound (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)-amino]-pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid, and its calcium and sodium salts are disclosed in European Patent Application, Publication No. EP-A-0521471, and in Bioorganic and Medicinal Chemistry, (1997), 5(2), 437-444. This latter statin is now known under its generic name rosuvastatin.

10

In the present application, the term "cholesterol-lowering agent" also includes chemical modifications of the HMG-CoA reductase inhibitors, such as esters, prodrugs and metabolites, whether active or inactive.

15 The present invention also includes a compound of the present invention in combination with a bile acid sequestering agent, for example colestipol or cholestyramine or cholestagel.

The present invention also includes a compound of the present invention in combination with an inhibitor of the ileal bile acid transport system (IBAT inhibitor).

20

Suitable compounds possessing IBAT inhibitory activity have been described, see for instance the compounds described in WO 93/16055, WO 94/18183, WO 94/18184, WO 96/05188, WO 96/08484, WO 96/16051, WO 97/33882, WO 98/07449, WO 98/03818, WO 98/38182, WO 99/32478, WO 99/35135, WO 98/40375, WO 99/35153, WO 99/64409, WO 99/64410,  
25 WO 00/01687, WO 00/47568, WO 00/61568, WO 00/62810, WO 01/68906, DE 19825804, WO 00/38725, WO 00/38726, WO 00/38727, WO 00/38728, WO 00/38729, WO 01/68906, WO 01/66533, WO 02/32428, WO 02/50051, EP 864 582, EP489423, EP549967, EP573848, EP624593, EP624594, EP624595 and EP624596 and the contents of these patent applications are incorporated herein by reference.

30

Particular classes of IBAT inhibitors suitable for use in the present invention are benzothiepinines, and the compounds described in the claims, particularly claim 1, of WO



00/01687, WO 96/08484 and WO 97/33882 are incorporated herein by reference. Other suitable classes of IBAT inhibitors are the 1,2-benzothiazepines, 1,4-benzothiazepines and 1,5-benzothiazepines. A further suitable class of IBAT inhibitors is the 1,2,5-benzothiadiazepines.

5

One particular suitable compound possessing IBAT inhibitory activity is (3*R*,5*R*)-3-butyl-3-ethyl-1,1-dioxo-5-phenyl-2,3,4,5-tetrahydro-1,4-benzothiazepin-8-yl  $\beta$ -D-glucopyranosiduronic acid (EP 864 582). Other suitable IBAT inhibitors include one of:

- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(carboxymethyl) carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N'*-(carboxymethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(2-sulphoethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 15 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(2-sulphoethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N'*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N'*-(2-sulphoethyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 20 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N'*-(2-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N'*-(2-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 25 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N'*-(5-carboxypentyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N'*-(2-carboxyethyl)carbamoyl] benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{ $\alpha$ -[*N'*-(2-sulphoethyl)carbamoyl]-2-fluorobenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 30 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N'*-(R)-(2-hydroxy-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N'*-(R)-(2-hydroxy-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)- $\alpha$ -(*N'*-{(R)-1-[*N''*-(R)-(2-hydroxy-1-carboxyethyl)carbamoyl]-2-hydroxyethyl}carbamoyl)benzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{ $\alpha$ -[*N'*-(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{ $\alpha$ -[*N'*-((ethoxy)(methyl)phosphorylmethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-{*N*-[(R)- $\alpha$ -(*N'*-{2-[(hydroxy)(methyl)phosphoryl]ethyl}carbamoyl)benzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N'*-(2-methylthio-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)- $\alpha$ -(*N'*-{2-[(methyl)(ethyl)phosphoryl]ethyl}carbamoyl)-4-hydroxybenzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)- $\alpha$ -(*N'*-{2-[(methyl)(hydroxy)phosphoryl]ethyl}carbamoyl)-4-hydroxybenzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[(R)-*N'*-(2-methylsulphinyl-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methoxy-8-[*N*-{(R)- $\alpha$ -[*N'*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N*-((R)-1-carboxy-2-methylthioethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N*-((S)-1-carboxybutyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N*-((S)-1-carboxypropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N*-((S)-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N*-((S)-1-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N*-((R)-1-carboxy-2-methylthioethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N*-{(S)-1-[*N*-((S)-2-hydroxy-1-carboxyethyl)carbamoyl]propyl}carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
- 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
- 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)- $\alpha$ -[*N*-((S)-1-carboxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-(*R/S*)- $\alpha$ -{*N*-[1-(*R*)-2-(*S*)-1-hydroxy-1-(3,4-dihydroxyphenyl)prop-2-yl]carbamoyl}-4-hydroxybenzyl)carbamoylemethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)- $\alpha$ -[*N*-(2-(*S*)-3-(*R*)-4-(*R*)-5-(*R*)-2,3,4,5,6-pentahydroxyhexyl)carbamoyle]-4-hydroxybenzyl)carbamoylemethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; and

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)- $\alpha$ -[*N*-(2-(*S*)-3-(*R*)-4-(*R*)-5-(*R*)-2,3,4,5,6-pentahydroxyhexyl)carbamoyle]benzyl)carbamoylemethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to an additional further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the present invention optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration one or more of the following agents selected from:

- a CETP (cholesteryl ester transfer protein) inhibitor, for example those referenced and described in WO 00/38725 page 7 line 22 - page 10, line 17 which are incorporated herein by reference;
- a cholesterol absorption antagonist for example azetidinones such as SCH 58235 and those described in US 5,767,115 which are incorporated herein by reference;
- a MTP (microsomal transfer protein) inhibitor for example those described in Science, 282, 751-54, 1998 which are incorporated herein by reference;
- a nicotinic acid derivative, including slow release and combination products, for example, nicotinic acid (niacin), acipimox and niceritrol;
- a phytosterol compound for example stanols;
- probucol;
- an omega-3 fatty acid for example Omacor<sup>TM</sup>;
- an anti-obesity compound for example orlistat (EP 129,748) and sibutramine (GB 2,184,122 and US 4,929,629);
- an antihypertensive compound for example an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, an andrenergic blocker, an alpha andrenergic

blocker, a beta andrenergic blocker for example metoprolol, a mixed alpha/beta andrenergic blocker, an andrenergic stimulant, calcium channel blocker, an AT-1 blocker, a saluretic, a diuretic or a vasodilator;  
a CB1 antagonist or inverse agonist for example as described in WO01/70700 and EP 65635 ;  
5 aspirin;  
a Melanin concentrating hormone (MCH) antagonist;  
a PDK inhibitor; or  
modulators of nuclear receptors for example LXR, FXR, RXR, and RORalpha;  
or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof,  
10 optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Particular ACE inhibitors or pharmaceutically acceptable salts, solvates, solvate of such salts or a prodrugs thereof, including active metabolites, which can be used in combination with a  
15 compound of the invention include but are not limited to, the following compounds: alacepril, alatriopril, altiopril calcium, ancovenin, benazepril, benazepril hydrochloride, benazeprilat, benzoylcaptopril, captopril, captopril-cysteine, captopril-glutathione, ceranapril, ceranopril, ceronapril, cilazapril, cilazaprilat, delapril, delapril-diacid, enalapril, enalaprilat, enapril, epicaptopril, foroxymithine, fosfenopril, fosenopril, fosenopril sodium, fosinopril, fosinopril  
20 sodium, fosinoprilat, fosinoprilic acid, glycopril, hemorphin-4, idrapril, imidapril, indolapril, indolaprilat, libenzapril, lisinopril, lyciumin A, lyciumin B, mixanpril, moexipril, moexiprilat, moveltipril, muracein A, muracein B, muracein C, pentopril, perindopril, perindoprilat, pivalopril, pivopril, quinapril, quinapril hydrochloride, quinaprilat, ramipril, ramiprilat, spirapril, spirapril hydrochloride, spiraprilat, spiropril, spiropril hydrochloride, temocapril,  
25 temocapril hydrochloride, teprotide, trandolapril, trandolaprilat, utibapril, zabicipril, zabiciprilat, zofenopril and zofenoprilat. Preferred ACE inhibitors for use in the present invention are ramipril, ramiprilat, lisinopril, enalapril and enalaprilat. More preferred ACE inhibitors for uses in the present invention are ramipril and ramiprilat.

Preferred angiotensin II antagonists, pharmaceutically acceptable salts, solvates, solvate of  
30 such salts or a prodrugs thereof for use in combination with a compound of the invention include, but are not limited to, compounds: candesartan, candesartan cilexetil, losartan, valsartan, irbesartan, tasosartan, telmisartan and eprosartan. Particularly preferred angiotensin

II antagonists or pharmaceutically acceptable derivatives thereof for use in the present invention are candesartan and candesartan cilexetil.

Therefore in an additional feature of the invention, there is provided a method for for the treatment of type 2 diabetes and its associated complications in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of the present invention in simultaneous, sequential or separate administration with an effective amount of one the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of the present invention of a compound of the invention in simultaneous, sequential or separate administration with an effective amount of one the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the present invention and one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of the present invention and one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of the present invention in a first unit dosage form;

b) one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

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According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of the present invention together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;

b) one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the present invention of the present invention and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of metabolic syndrome or type 2 diabetes and its associated complications in a warm-blooded animal, such as man.

20

According to another feature of the invention there is provided the use of a compound of the present invention and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the present invention optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a

pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

### Experimental

<sup>1</sup>H NMR and <sup>13</sup>C NMR measurements were performed on a Varian Mercury 300 or Varian UNITY plus 400, 500 or 600 spectrometers, operating at <sup>1</sup>H frequencies of 300, 400, 500 and 600 MHz, respectively, and at <sup>13</sup>C frequencies of 75, 100, 125 and 150 MHz, respectively. Measurements were made on the delta scale ( $\delta$ ).

Unless otherwise stated, chemical shifts are given in ppm with the solvent as internal standard.

X-ray powder diffraction analysis (XRPD) was performed using variable slits on samples prepared according to standard methods without using any internal standard. Standard methods are described in, for example, Giacovazzo, C. *et al* (1995), *Fundamentals of Crystallography*, Oxford University Press; Jenkins, R. and Snyder, R. L. (1996), *Introduction to X-Ray Powder Diffraction*, John Wiley & Sons, New York; Bunn, C. W. (1948), *Chemical Crystallography*, Clarendon Press, London; or Klug, H. P. & Alexander, L. E. (1974), *X-ray Diffraction Procedures*, John Wiley and Sons, New York. X-ray analyses were performed using Cu-radiation on a Siemens D5000 diffractometer. The X-axis in the figures below is 2-theta and the Y-axis is intensity.

Differential scanning calorimetry (DSC) was performed using a Mettler DSC820 or a Mettler DSC820E, according to standard methods, for example those described in Höhne, G. W. H. *et al* (1996), *Differential Scanning Calorimetry*, Springer, Berlin.

Thermo-gravimetric analysis (TGA) was performed using a Mettler Toledo TGA850 or a Mettler Toledo TG851.

It will be appreciated by the skilled person that crystalline forms of compounds of the invention may be prepared by analogy with processes described herein and/or in accordance with the Examples below, and may show essentially the same XRPD diffraction patterns



and/or DSC and/or TGA thermograms as those disclosed herein. By “essentially the same” XRPD diffraction patterns and/or DSC and/or TGA thermograms, we include those instances when it is clear from the relevant patterns and/or thermograms (allowing for experimental error) that essentially the same crystalline form has been formed. When provided, DSC onset  
5 temperatures may vary in the range  $\pm 5^{\circ}\text{C}$  (e.g.  $\pm 2^{\circ}\text{C}$ ), and XRPD distance values may vary in the range  $\pm 2$  on the last decimal place. It will be appreciated by the skilled person that XRPD intensities may vary when measured for essentially the same crystalline form for a variety of reasons including, for example, preferred orientation

#### 10 Abbreviations

DMSO	dimethyl sulfoxide
EtOAc	ethyl acetate
DMF	<i>N,N</i> -dimethylformamide
THF	tetrahydrofuran
15 MeCN	acetonitrile
MeOH	methanol
TFA	trifluoroacetic acid
NH <sub>4</sub> OAc	ammonium acetate
t	triplet
20 s	singlet
d	doublet
q	quartet
m	multiplet
bs	broad singlet
25 XRPD	X-ray powder diffraction
TGA	thermogravimetric analysis
DSC	differential scanning calorimetry

#### Examples

##### 30 Preparation of Acid starting material

##### (i) Methyl 2-chloro-3-[4-(2-hydroxyethyl)phenyl]propanoate

2-(4-Aminophenyl)ethanol (11g, 81mmol) and 32ml conc HCl was dissolved in acetone and cooled to 0°C. Sodium nitrite (5.6g, 81mmol) in 20ml water was added dropwise. The temperature was kept under 0°C. After one hour, methyl acrylate (70g, 808mmol) and CuI (1.6g, 8mmol) were added (<0°C). The reaction mixture was stirred at room temperature  
 5 overnight.

The solvent was evaporated and water was added. The water phase was extracted three times with EtOAc, the organic phases were pooled and washed with water, dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The crude product was purified by flash chromatography using a 65:35 mixture of EtOAc and heptane as eluent. Further purification by preparative  
 10 HPLC (using a gradient of CH<sub>3</sub>CN/ 5%CH<sub>3</sub>CN-waterphase containing 0.1M NH<sub>4</sub>OAc as eluent) gave 9.7g product (yield 49%) as an oil.

<sup>1</sup>HNMR ( 400MHz, CDCl<sub>3</sub>): 2.84 (t, 3H), 3.15 (dd, 1H), 3.35 (dd, 1H), 3.75 (s, 3H), 3.84 (t, 3H), 4.43 (t, 1H), 7.17 (d, 4H)

15 (ii) Methyl 3-(4-{2-[4-(benzyloxy)phenoxy]ethyl}phenyl)-2-chloropropanoate

Triphenylphosphine (2.4g, 9mmol) was added to a solution of methyl 2-chloro-3-[4-(2-hydroxyethyl)phenyl]propanoate (2.1g, 8.5mmol) and 4-(benzyloxy)phenol (1.7g, 8mmol) in 20ml toluene under nitrogen atmosphere. The solution was warmed to 55°C and diisopropyl  
 20 azodicarboxylate (1.8g, 9mmol) was added. The reaction mixture was stirred at 55°C overnight.

The mixture was allowed to cool and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography using a 80:20 mixture of heptane and EtOAc as eluent to yield 2.28g of the desired product (yield 61%) as colourless crystals.  
 25 <sup>1</sup>HNMR (400MHz, CDCl<sub>3</sub>): 3.05 (t, 2H), 3.16 (dd, 1H), 3.36 (dd, 1H), 3.75 (s, 3H), 4.12 (t, 2H), 4.45 (t, 1H), 5.01 (s, 2H), 6.82 (m, 2H), 6.90 (m, 2H), 7.13-7.27 (m, 4H), 7.29- 7.47 (m, 5H).

(iii) Methyl 2-chloro-3-{4-[2-(4-hydroxyphenoxy)ethyl]phenyl}propanoate

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Methyl 3-(4-{2-[4-(benzyloxy)phenoxy]ethyl}phenyl)-2-chloropropanoate (1.0g, 2.4mmol) and dimethyl sulfide (0.9g, 14mmol) was dissolved in 60ml CH<sub>2</sub>Cl<sub>2</sub>. Boron trifluoride

etherate (2.0g, 14mmol) was added dropwise to the stirred solution. The reaction mixture was stirred for two days at room temperature. Another equivalent (0.4g, 2.87mmol) boron trifluoride etherate was added and the stirring was continued overnight.

Water was added. The phases were separated and the aqueous phase was extracted twice with  
5 CH<sub>2</sub>Cl<sub>2</sub>. The organic phases were pooled, washed (water, brine), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. Further purification by preparative HPLC using a gradient of CH<sub>3</sub>CN/ 5% CH<sub>3</sub>CN-waterphase containing 0.1M NH<sub>4</sub>OAc gave 0.55g of the desired product (yield 52%) as an oil.

<sup>1</sup>HNMR (400MHz, CDCl<sub>3</sub>): 3.04 (t, 2H), 3.16 (dd, 1H), 3.35 (dd, 1H), 3.75 (s, 3H), 4.10 (t,  
10 2H), 4.40 (t, 1H), 6.75 (m, 4H), 7.12-7.29 (m, 4H).

(iv) Methyl 2-chloro-3-[4-(2-[4-[(methylsulfonyl)oxy]phenoxy]ethyl)phenyl]propanoate

Methyl 2-chloro-3-[4-[2-(4-hydroxyphenoxy)ethyl]phenyl]propanoate (334mg, 1.0mmol)  
15 and triethylamine (303mg, 3.0mmol) was dissolved in 20ml dichlormethane and cooled to -20°C under nitrogen atmosphere. Methanesulfonyl chloride (114mg, 1.0mmol) was added dropwise. The mixture was allowed to reach room temperature. After 2 hours dichlormethane was added, the mixture was washed (water, brine), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to yield 394mg pure product (yield 96%).

20 <sup>1</sup>HNMR (400MHz, CDCl<sub>3</sub>): 3.02-3.11 (m, 5H), 3.15 (dd, 1H), 3.35 (dd, 1H), 3.74 (s, 3H), 4.14 (t, 2H), 4.44 (t, 1H), 5.29 (s, 2H), 6.88 (d, 2H), 7.14-7.25 (m, 6H).

(v) Methyl 2-({2-[4-(benzyloxy)phenyl]ethyl}thio)-3-[4-(2-[4-[(methylsulfonyl)oxy]phenoxy]ethyl)phenyl]propanoate

25 2-[4-(Benzyloxy)phenyl]ethanethiol (334mg, 1.4mmol), methyl 2-chloro-3-[4-(2-[4-[(methylsulfonyl)oxy]phenoxy]ethyl)phenyl]propanoate (394mg, 0.95mmol) and potassium carbonate (189mg, 1.4mmol) were dissolved in 14ml dry DMF and stirred under nitrogen atmosphere at room temperature overnight.

30 The solvent was evaporated under reduced pressure and the residue was dissolved in toluene. The organic phase was washed (water, brine), dried (MgSO<sub>4</sub>) and evaporated. Further purification by preparative HPLC using a gradient of CH<sub>3</sub>CN/5% CH<sub>3</sub>CN-waterphase containing 0.1M NH<sub>4</sub>OAc gave 477mg of the desired product (yield 75%).

<sup>1</sup>HNMR (400MHz, CDCl<sub>3</sub>): 2.76-2.89 (m, 4H), 2.95 (dd, 1H), 3.09 (m, 5H), 3.20 (dd, 1H), 3.53 (m, 1H), 3.70 (s, 3H), 4.15 (t, 2H), 5.06 (s, 2H), 6.91 (m, 4H), 7.07-7.24 (m, 8H), 7.31-7.48 (m, 5H).

5 (vi) Methyl 2-([2-(4-hydroxyphenyl)ethyl]thio)-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoate

To a solution of methyl 2-([2-[4-(benzyloxy)phenyl]ethyl]thio)-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoate (477mg, 0.8mmol) and 15ml  
10 dichlormethane, dimethyl sulfide (239mg, 3.8mmol) and boron trifluoride etherate (545mg, 3.8mmol) were added. After 18 hours of stirring water was added to the reaction. The phases were separated and the aqueous phase was extracted twice with dichlormethane. The organic phases were pooled, dried (MgSO<sub>4</sub>) and evaporated under reduced pressure.

274mg of the desired product (yield 67%) was obtained as an oil.

15 <sup>1</sup>HNMR (400MHz, CDCl<sub>3</sub>): 2.70-2.85 (m, 4H), 2.91 (dd, 1H), 3.05 (t, 2H), 3.10 (s, 3H), 3.17 (dd, 1H), 3.49 (m, 1H), 3.68 (s, 3H), 4.13 (t, 2H), 6.72 (d, 2H), 6.87 (d, 2H), 6.99 (d, 2H), 7.10-7.22 (m, 6H)

20 (vii) 2-([2-(4-Hydroxyphenyl)ethyl]thio)-3-[4-(2-{4-[(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]propanoic acid

Methyl 2-([2-(4-hydroxyphenyl)ethyl]thio)-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}-ethyl)phenyl]propanoate (105mg, 0.2mmol) was dissolved in 6.5ml of a 7:1 mixture of THF and water and cooled on an ice-bath. Lithium hydroxide (9.4mg, 0.4mmol) was added. Water  
25 was added to the reaction mixture after 24 hours of stirring at room temperature. The THF was evaporated under reduced pressure and the residue was acidified with 1M hydrochloric acid. The water phase was extracted with EtOAc (x3), the organic phases were pooled, washed (water, brine), dried (MgSO<sub>4</sub>) and evaporated. The crude product was purified using preparative HPLC (eluent: CH<sub>3</sub>CN / 5% CH<sub>3</sub>CN-waterphase containing 0.1M NH<sub>4</sub>OAc) to  
30 give 74mg of the desired product (yield 97%) as an oil.

<sup>1</sup>HNMR (400MHz, CDCl<sub>3</sub>): 2.68-2.95 (m, 5H), 3.05 (t, 2H), 3.10 (s, 3H), 3.17 (dd, 1H), 3.47 (m, 1H), 4.12 (t, 2H), 6.70 (d, 2H), 6.86 (d, 2H), 6.97 (d, 2H), 7.12-7.21 (m, 6H).

$^{13}\text{C}$ NMR (100MHz,  $\text{CDCl}_3$ ): 33.8, 35.1, 35.5, 37.2, 37.3, 48.1, 69.3, 115.6, 115.8, 123.3, 129.3, 129.4, 129.9, 132.3, 136.2, 136.9, 142.8, 154.4, 158.0, 177.2.

5 (viii) (-)-2-([2-(4-hydroxyphenyl)ethyl]thio)-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid

The racemate of 2-([2-(4-hydroxyphenyl)ethyl]thio)-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid was separated into its enantiomers using chiral  
 10 chromatography. A Chiralpak AD JDB01+ AS003 (336 x 100 mm i.d.) and ethanol/formic acid 100/0.01% was used as mobile phase. The racemate (9 g) was dissolved in ethanol and injected onto the column. The first eluting peak was collected and UV-detected. The product (4.1 g) was obtained with an enantiomeric purity >99%. The optical rotation was found to be  $[\alpha]^{20}_{\text{D}} = -33^\circ$  by dissolving the enantiomer in methanol to give a concentration of 0.64  
 15 g/100ml. The optical rotation was measured at 20 °C using the sodium line at 589 nm.  
 $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ ): 7.17-7.22 (6H, m), 6.99 (2H, d), 6.94 (2H, d), 6.69 (2H, d), 4.17 (2H, t), 3.46 (1H, t), 3.16 (3H, s), 3.13 (1H, dd), 3.05 (2H, t), 2.69-2.88 (5H, m).

**Example 1**

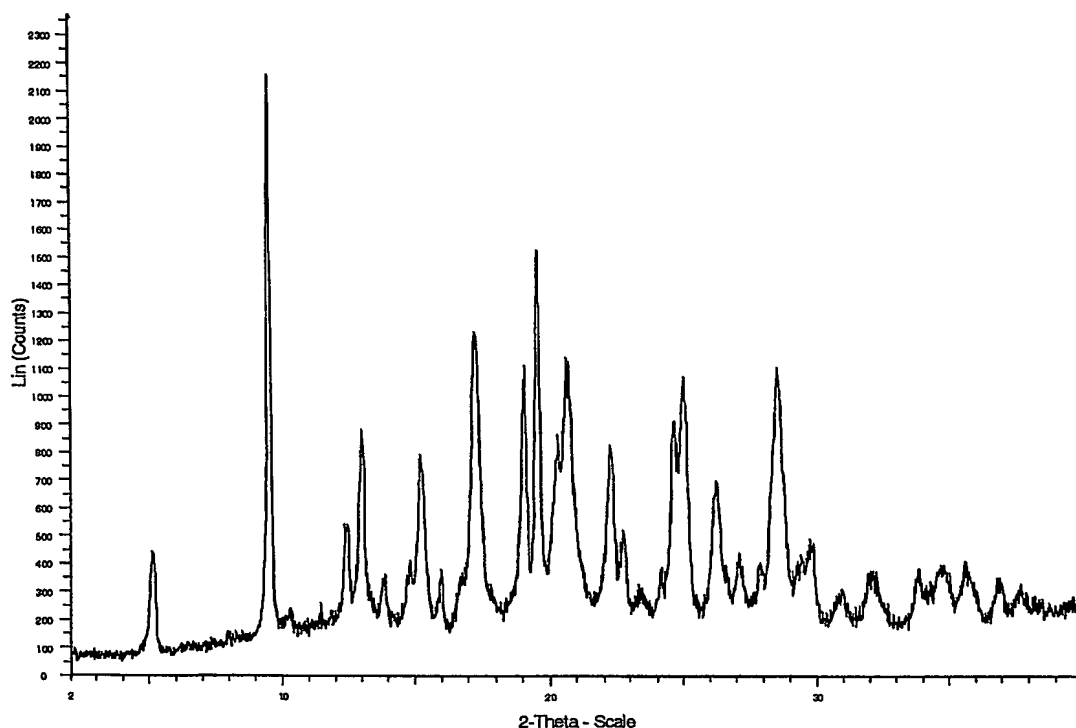
20 Potassium salt of (-)-2-([2-(4-Hydroxyphenyl)ethyl]thio)-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid

A solution of (S)-2-([2-(4-hydroxyphenyl)ethyl]thio)-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid (344g) in ethanol (8.2 L) was neutralised with  
 25 addition of ethanolic 4.2% w/w potassium hydroxide solution (1.2 L). The neutralised solution was heated to 50°C and screened into a crystalliser vessel. The solution was reduced in volume to 4.4 L by distillation. Whilst still hot at 50°C, toluene (6.2 L) was added as co-solvent. The batch was allowed to cool to ambient temperature and seeded. Further toluene (4.2 L) was added to the crystallised solution. The slurry was chilled to -5°C over 60 minutes  
 30 and held for a further 150 minutes. The product was isolated by filtration and washed with chilled toluene. The reaction afforded title compound as an off white solid in 339g yield.

The X-axis in the figures below is below is 2-theta and the Y axis is intensity.

DSC showed an endotherm with an extrapolated onset temperature in the range of 91-97°C. TGA showed a weight loss in the range of 6.0-7.1 % w/w between 25-110°C. DSC analysis repeated on purer sample may give a higher melting point.

Crystals of the potassium salt of (S)-2-[[2-(4-hydroxyphenyl)ethyl]thio]-3-[4-(2-{4-  
5 [(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]propanoic acid (obtained by way of the example above and/or by other ways) were analyzed by XRPD and the results are tabulated below and are shown in Figure A.



10 Figure A, XRPD pattern of potassium salt of (S)-2-[[2-(4-hydroxyphenyl)ethyl]thio]-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid

d-value (Angstrom)	intensity (rel)
17.4	w
9.3	vs
7.1	w
6.8	m
6.4	w

5.8	m
5.1	m
4.65	m
4.53	s
4.29	m
3.99	w
3.91	w
3.61	w
3.55	m
3.39	w
3.12	m

### Example 2

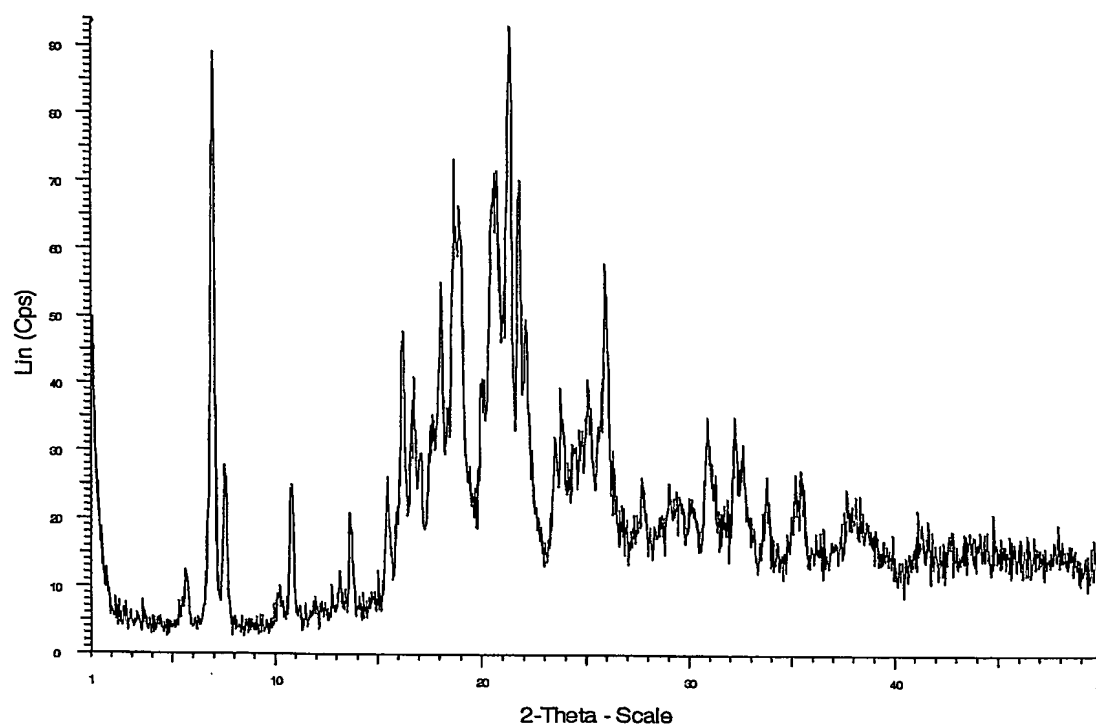
Sodium salt of (-)-2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]-  
5 phenoxy}ethyl)phenyl]propanoic acid

(-)-2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]-  
phenoxy}ethyl)phenyl]propanoic acid (529mg) was dissolved in ethanol (3.2 ml). The  
solution was heated to 45°C and sodium methoxide (58mg, 1.03 eq.) was added. Then, the  
10 solution was heated to 60°C and toluene was added (4 ml). After this, the solution was cooled  
at 0 °C for 18 hours. The solid was collected by filtration, washed with toluene (2x0.5  
ml).and dried in vacuo at 50 °C to give the title compound (205 mg) as crystals.

Examples of Properties of a sodium salt of (-)-2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-  
15 {4-[(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]propanoic acid  
DSC showed an endotherm with an extrapolated onset temperature of 155°C. TGA showed a  
weight loss of 0.3 % w/w between 25-110°C and 0.7% w/w between 110-165°C. DSC  
analysis repeated on purer sample may give a higher melting point. Crystals of the sodium  
salt of (S)-2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]-  
20 phenoxy}ethyl)phenyl]propanoic acid (obtained by way of the example above and/or by other  
ways) were analyzed by XRPD and the results are tabulated below and are shown in Figure B.

Figure B.XRPD pattern of sodium salt of (-)-2-[[2-(4-hydroxyphenyl)ethyl]thio]-3-[4-(2-{4-[(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]propanoic acid

5



d-value (Angstrom)	intensity (rel)
15.9	w
12.8	s
11.8	m
8.2	m
6.5	w
5.7	m
5.5	m
5.3	m
4.91	m
4.74	m



4.68	m
4.30	m
4.16	s
4.08	m
4.01	w
3.78	w
3.73	w
3.55	w
3.43	m
2.89	w
2.77	w
2.65	w

### Biological activity

#### Formulations

- 5 Compounds were dissolved in DMSO to obtain 16 mM stock solutions. Before assays, stock solutions were further diluted in DMSO and culture media.

#### GENERAL CHEMICALS AND REAGENTS

- Luciferase assay reagent was purchased from Packard, USA. Restriction Enzymes were from  
10 Boehringer and Vent polymerase from New England Biolabs.

#### CELL LINES AND CELL CULTURE CONDITIONS

- U2-OS, (Osteogenic sarcoma, Human) was purchased from ATCC, USA. Cells were expanded and refrozen in batches from passage number six. Cells were cultured in Dulbecco's  
15 modified Eagle medium (DMEM) with 25 mM glucose, 2 mM glutamine or 4 mM L-alanyl-L-glutamine, 10% fetal calf serum, at 5% CO<sub>2</sub>. Phosphate buffered saline (PBS) without addition of calcium or magnesium was used. All cell culture reagents were from Gibco (USA) and 96-well cell culture plates were purchased from Wallach.

## PLASMID CONSTRUCTS FOR HETEROLOGOUS EXPRESSION

Standard recombinant DNA techniques were carried out as described by Ausubel (7). The Luciferase reporter vector, pGL5UAS (clone consists of five copies of the GAL4 DNA binding sequence, 5'-CGACGGAGTACTGTCCTCCGAGCT-3', cloned into the SacI/XhoI sites of pGL3-Promoter (Promega). The SacI/XhoI fragment carrying the UAS sites was constructed using annealed overlapping oligonucleotides.

Expression vectors used are based upon pSG5 (Stratagene). All vectors contain an EcoRI/NheI fragment encoding the DNA binding domain of GAL4 (encoding amino acid positions 1-145 of database accession number P04386) followed by an in-frame fusion to a fragment encoding the nuclear localisation sequence from T antigen of Polyoma Virus. The nuclear localisation sequence was constructed using annealed overlapping oligonucleotides creating NheI/KpnI sticky ends (5'-CTAGCGCTCCTAGAAGAAACGCAAGGTTGGTAC-3'). The ligand binding domains from human and mouse PPAR $\alpha$  and human and mouse PPAR $\gamma$  were PCR amplified as KpnI/BamHI fragments and cloned in frame to the GAL4 DNA binding domain and the nuclear localisation sequence. The sequence of all plasmid constructs used were confirmed by sequencing.

The following expression vectors were used for transient transfections:

vector	encoded PPAR subtype	sequence reference <sup>1</sup>
pSGGALhPPa	human PPAR $\alpha$	S74349, nt 625-1530
pSGGALmPPa	murine PPAR $\alpha$	X57638, nt 668-1573
pSGGALhPPg	human PPAR $\gamma$	U63415, nt 613-1518
pSGGALmPPg	murine PPAR $\gamma$	U09138, nt 652-1577

<sup>1</sup> refers to nucleotide positions of data base entry used to express the ligand binding domain.

## TRANSIENT TRANSFECTIONS

Frozen stocks of cells from passage number six were thawed and expanded to passage number eight before transfections. Confluent cells were trypsinised, washed and pelleted by centrifugation at 270xg for 2 minutes. The cell pellet was resuspended in cold PBS to a cell concentration of about  $18 \times 10^6$  cells/ml. After addition of DNA, the cell suspension was incubated on ice for approximately 5 minutes before electroporation at 230 V, 960  $\mu$ F in Biorad's Gene Pulser<sup>TM</sup> in 0.5 ml batches. A total of 50  $\mu$ g DNA was added to each batch of 0.5 ml cells, including 2.5  $\mu$ g expression vector, 25  $\mu$ g reporter vector and 22.5  $\mu$ g unspecific DNA (pBluescript, Stratagene).

10

After electroporation, cells were diluted to a concentration of 320'000 cells/ml in DMEM without phenol red, and approximately 25'000 cells/well were seeded in 96-well plates. In order to allow cells to recover, seeded plates were incubated at 37°C for 3-4 hours before addition of test compounds. In assays for PPAR $\alpha$ , the cell medium was supplemented with resin-charcoal stripped fetal calf serum (FCS) in order to avoid background activation by fatty acid components of the FCS. The resin-charcoal stripped FCS was produced as follows; for 500 ml of heat-inactivated FCS, 10 g charcoal and 25 g Bio-Rad Analytical Grade Anion Exchange Resin 200-400 mesh were added, and the solution was kept on a magnetic stirrer at room temperature over night. The following day, the FCS was centrifuged and the stripping procedure was repeated for 4-6 hours. After the second treatment, the FCS was centrifuged and filter sterilised in order to remove remnants of charcoal and resin.

20

## ASSAY PROCEDURE

Stock solutions of compounds in DMSO were diluted in appropriate concentration ranges in master plates. From master plates, compounds were diluted in culture media to obtain test compound solutions for final doses.

25

After adjustment of the amount of cell medium to 75  $\mu$ l in each well, 50  $\mu$ l test compound solution was added. Transiently transfected cells were exposed to compounds for about 24 hours before the luciferase detection assay was performed. For luciferase assays, 100  $\mu$ l of assay reagent was added manually to each well and plates were left for approximately 20

30

minutes in order to allow lysis of the cells. After lysis, luciferase activity was measured in a 1420 Multiwell counter, Victor, from Wallach.

#### Reference compounds

- 5 The TZD pioglitazone was used as reference substance for activation of both human and murine PPAR $\gamma$ . 5,8,11,14-Eicosatetrayonic acid (ETYA) was used as reference substance for human PPAR $\alpha$ .

#### Calculations and analysis

- 10 For calculation of EC<sub>50</sub> values, a concentration-effect curve was established. Values used were derived from the average of two or three independent measurements (after subtraction of the background average value) and were expressed as the percentage of the maximal activation obtained by the reference compound. Values were plotted against the logarithm of the test compound concentration. EC<sub>50</sub> values were estimated by linear intercalation between  
15 the data points and calculating the concentration required to achieve 50% of the maximal activation obtained by the reference compound.

The compounds of the present invention have an EC<sub>50</sub> of less than 5 $\mu$ mol/l for PPAR $\alpha$ . Additionally the ratio of the EC<sub>50</sub> (PPAR $\gamma$ ) : EC<sub>50</sub> (PPAR $\alpha$ ) is greater than 25:1. It is  
20 believed that this ratio is important with respect to the pharmacological activity of the compounds and to their therapeutic profile.

In addition the compounds of the present invention exhibit improved DMPK (Drug Metabolism and Pharmacokinetic) properties for example they exhibit improved metabolic  
25 stability *in vitro*. The compounds also have a promising toxicological profile.

**Claims:**

1. A potassium salt or a sodium salt of (-)-2-[[2-(4-hydroxyphenyl)ethyl]thio]-3-[4-(2-{4-  
5 [(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid.
2. A salt as claimed in claim 1 which may be a solvate, a hydrate, a mixed solvate/hydrate ,  
an ansolvate or an anhydrate.
- 10 3. A salt as claimed in claim 1 or claim 2 in crystalline or partially crystalline form.
4. A pharmaceutical formulation comprising a compound according to any one of claims 1  
to 3 in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.
- 15 5. A method of treating or preventing lipid disorders (dyslipidemia) whether or not  
associated with insulin resistance comprising the administration of a compound according to  
any one of claims 1 to 3 to a mammal in need thereof.
6. The use of a compound according to any one of claims 1 to 3 in the manufacture of a  
20 medicament for the treatment of lipid disorders (dyslipidemia) whether or not associated with  
insulin resistance.
7. A method of treating or preventing type 2 diabetes comprising the administration of an  
effective amount of a compound according to any one of claims 1 to 3 to a mammal in need  
25 thereof.
8. A pharmaceutical composition comprising a compound according to any one of claims 1  
to 3 combined with another therapeutic agent that is useful in the treatment of disorders  
associated with the development and progress of atherosclerosis such as hypertension,  
30 hyperlipidaemias, dyslipidaemias, diabetes and obesity.

**ABSTRACT**

5

**Title : Therapeutic Agents**

A potassium salt or a sodium salt of (-)-2-[[2-(4-hydroxyphenyl)ethyl]thio]-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid, processes for their  
10 preparation, their use in treating clinical conditions including lipid disorders (dyslipidemias) whether or not associated with insulin resistance and other manifestations of the metabolic syndrome, and pharmaceutical compositions containing them.